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Gonadal (Ovarian) Dysgenesis in 46,XX Individuals: Frequency of the Autosomal Recessive Form

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Gonadal (ovarian) dysgenesis with normal chromosomes (46,XX) clearly is a heterogeneous condition. In some forms, the defect is restricted to the gonads, whereas other affected females show neurosensory hearing loss (Perrault syndrome). In another form, brothers may have germ cell aplasia [Granat et al., *Fertil Steril* 1983; 40:215–219]. Nongenetic causes exist as well. To elucidate the proportion of XX gonadal (ovarian) dysgenesis due to autosomal recessive genes, we analyzed published (N = 17) and unpublished (N = 8) families having at least two female offspring. Analysis was restricted to cases in whom ovarian failure was documented by the presence of streak ovaries (published cases) or elevated gonadotropins (unpublished cases). We reasoned that the closer to that segregation ratio expected for an autosomal recessive trait (0.25), the lower the frequency of nongenetic forms. Segregation analysis utilized standard correction for single ascertainment, with only females included in the preliminary analysis. The segregation ratio estimate was 0.16. Our results suggest that many 46,XX females with gonadal (ovarian) dysgenesis represent a disorder segregating as an autosomal recessive trait, placing sisters of these cases at a 25% risk for this disorder.

KEY WORDS: XX gonadal (ovarian) dysgenesis, segregation analysis, autosomal recessive

INTRODUCTION

Phenotypic females with gonadal (ovarian) dysgenesis and normal chromosomes are considered to have "XX gonadal (ovarian) dysgenesis" [Simpson et al., 1971]. Such individuals usually present with lack of secondary sexual characteristics and/or failure of menarche due to streak ovaries and consequent estrogen deficiency. Endocrine studies show hypergonadotropic hypogonadism, i.e., elevated gonadotropin and decreased estrogen levels, as is characteristic of any individual with streak ovaries. Height is generally normal, with a mean height of 165 cm [Simpson, 1979].

Somatic anomalies are uncommon in XX gonadal (ovarian) dysgenesis; however, their presence in some families suggests heterogeneity. The most frequently observed somatic defect associated with XX gonadal (ovarian) dysgenesis is neurosensory hearing loss, a phenotype referred to as Perrault syndrome [Pallister and Opitz, 1979; McCarthy and Opitz, 1985; Nishi, 1988]. This is an autosomal recessive disorder. In other families, multiple sibs demonstrate gonadal (ovarian) dysgenesis and either an apparently unique pattern of associated somatic malformations [Maximillian, 1970; Hamet, 1973; Lundberg, 1976; Skre, 1976] or associated endocrine abnormalities [Sills et al., 1992]. These families suggest that different genes or alleles are responsible for the various phenotypes.

Excluding cases with somatic anomalies, the preserved multiple sibships with parental consanguinity support an autosomal recessive mutation as a cause in at least some cases [Giusti, 1966; Nazareth, 1977; Purandare, 1979]. XX gonadal (ovarian) dysgenesis also has been associated with infection, infiltrative diseases of the ovary (tuberculosis, β-thalassemia), autoimmune phenomena, and environmental agents affecting ovarian development [reviewed by Verp, 1983]. Whether XX gonadal (ovarian) dysgenesis without attendant somatic anomalies is due to an autosomal recessive gene or to nongenetic factors (phenocopies) is a dilemma in genetic counseling. That is, following the diagnosis of one affected child, should a couple be given a 25% recurrence risk for subsequent affected *female* offspring, or a considerably lower risk assuming the

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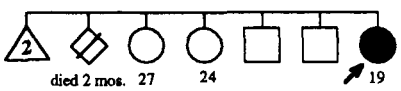
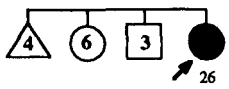
possibility of nongenetic phenocopies. To help address this question, we performed segregation analysis of 17 published and 8 unpublished cases of XX gonadal (ovarian) dysgenesis to determine the relative proportion of the autosomal recessive form.

MATERIALS AND METHODS

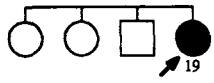
Cases were identified from two sources: cases published prior to 1982 and previously unpublished cases of the authors. All published cases had streak or hypoplastic ovaries documented visually by culdoscopy or laparoscopy [Aleem, 1981; Aubert, 1964; Boczkowski, 1970; Giusti et al., 1966; Landau et al., 1969; Laroche et al., 1964; Málková et al., 1974; McDonough et al., 1977; Moszkowski et al., 1965; Nazareth et al., 1977; Purandare and Sathe, 1979; Simpson et al., 1971; Slotnick, 1971; Vesely et al., 1980; Youlton et al., 1982]. Unpublished cases were ascertained from the clinical records of the Department of Obstetrics and Gynecology, Northwestern University, Chicago, IL (N = 7) and



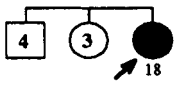
1. Aubert, 1964



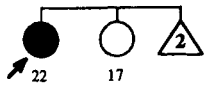
2. Laroche et al., 1964 (Case 2)



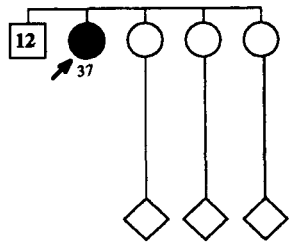
3. Moszkowski et al., 1965 (Case 2)



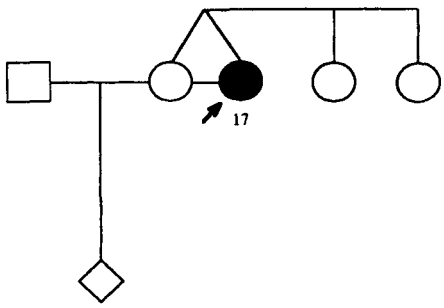
4. Landau et al., 1969



5. Simpson et al., 1971 (Patient 1)

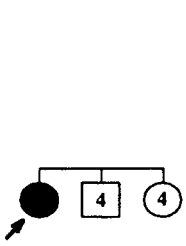


6. Simpson et al., 1971 (Patient 2)

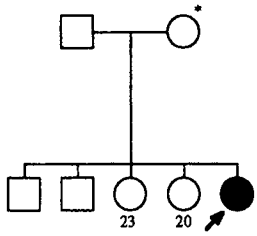


7. McDonough et al., 1977

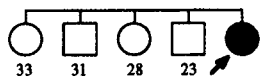
Fig. 1a. Singleton families, published. ●, Streak ovaries; ◐, streak/hypoplastic ovary; ⊗, premature ovarian failure; △, miscarriage; ⊘, deceased.



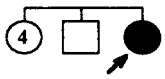
8. Northwestern University (Case 1)



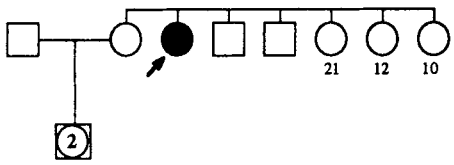
9. Northwestern University (Case 2)



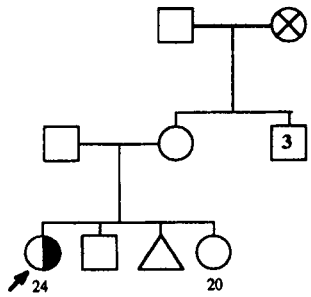
10. Northwestern University (Case 3)



11. Northwestern University (Case 4)



12. Northwestern University (Case 5)



13. University of Tennessee, Memphis (Case 6)

Fig. 1b. Singleton families, unpublished.

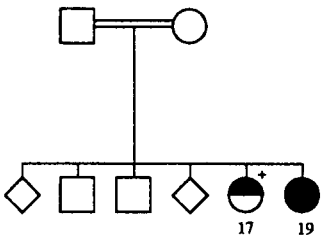
the Department of Pediatrics, University of Tennessee, Memphis (N = 1). In these cases, either gonadal visualization (N = 5) or elevated serum gonadotropins (>40 MIU/ml) (N = 3) was accepted as documentation of gonadal failure. Given current sensitivity of gonadotropin assays and rarity of other possible conditions (gonadotropin resistance), we reasoned that direct gonadal visualization is no longer necessary to confirm the presence of streak ovaries.

Cases in which chromosomal status was inferred from Barr body analysis were excluded, as were cases with somatic anomalies. In all included cases, a normal female karyotype (46,XX) was required. Blood leukocytes were analyzed in all cases. In some, additional tissues (i.e., skin fibroblasts, fascia streak gonad) were also studied. In only 4 of 20 cases were banding techniques reported. However, the major pitfall to be avoided is not minute deletions detectable only by 600–1200 band karyotypes, but rather failure to detect 45,X lines. This can be done as effectively with as without banding techniques.

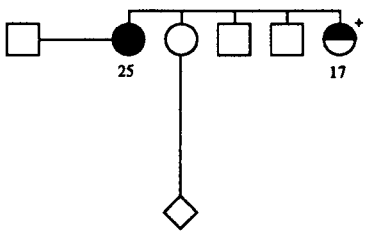
For utilization in the segregation analysis, information on number, sex, and ages or birth order of all sibs was also required. For sisters, either a stated history of normal menarche or evidence of fertility was necessary. Sisters younger than 16 were excluded from analysis unless menarche had occurred. To qualify as a potentially segregating sibship, at least one sister in addition to the proposita was necessary. Since the possible phenotypic effect of the gene in males has not been characterized, males were not included in the analysis.

Segregation Analysis

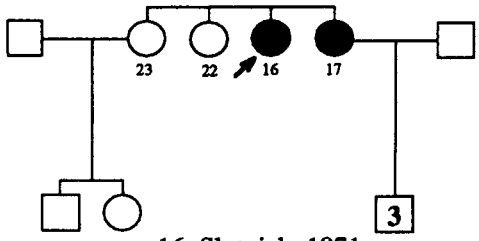
Segregation analysis is routinely utilized to test goodness-of-fit of observed segregation patterns and to estimate genetic parameters underlying different genetic models using family data. Ascertainment biases must be accounted for prior to analysis. Although bias can never be ruled out for published cases, we reason that bias should be minimized because all but one of the families included in this study were ascertained through a single proband. In the family reported by Purandare [1979], the method of ascertainment is unknown. For the families analyzed, ascertainment approaches single selection. Published cases may be bi-



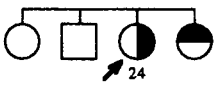
14. Giusti, 1966



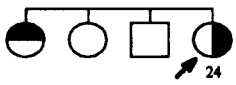
15. Boczkowski, 1970



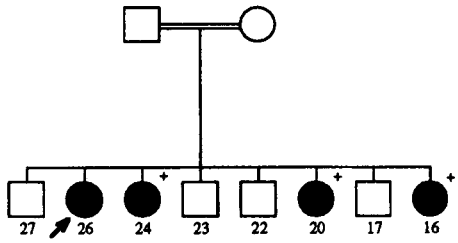
16. Slotnick, 1971



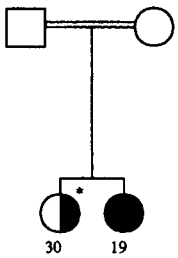
17. Málková, 1974
Family I



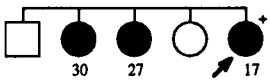
18. Málková et al., 1974
Family II



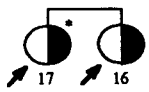
19. Nazareth et al., 1977



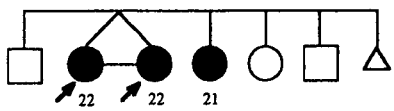
20. Purandare and Sathe, 1979



21. Vesley et al., 1980



22. Aleem, 1981

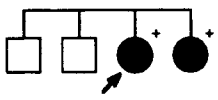


23. Youlton et al., 1982

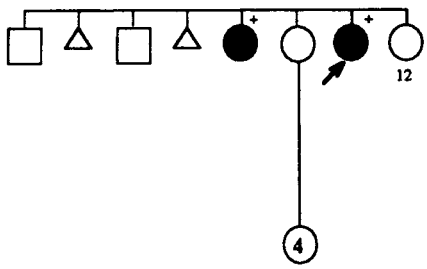
Fig. 2a. Multiplex families, published. ●, Streak ovaries; ◓, hypoplastic ovaries; ◐, streak/hypoplastic ovary; ⊗, premature ovarian failure; +, gonads not visualized; △, miscarriage; ⊘, deceased.

ased toward families with larger numbers of affected sibs; however, appropriate corrections for single selection can address this bias. Although it is expected that all individuals with XX gonadal (ovarian) dysgenesis would eventually seek medical care, the presence of a previously diagnosed relative surely increases the chance of ascertainment and subsequent publication. Therefore, the probability of two affected individuals in a single family being independently ascertained is minimal.

Using the SEGRAN computer program [Morton, 1959], maximum likelihood estimates were obtained



24. Northwestern University (Case 6)



25. Northwestern University (Case 7)

Fig. 2b. Multiplex families, unpublished.

for p, the segregation ratio, and x, the proportion of sporadic cases, while testing the fit of the proposed genetic model (e.g. recessive). The ideal model permits simultaneous estimation of parameters p and x, but in small data sets such as ours, it is sometimes impossible to achieve simultaneous estimation. In these situations, the model with the best, although not ideal fit, is chosen as the most probable.

RESULTS

Thirteen singleton families (seven published, six unpublished) (Fig. 1a,b) and 12 multiplex families (ten published, two unpublished) (Fig. 2a,b) were included in the analysis. The initial model of $p = 0.25$ (all cases recessive) and $x = 0$ (no sporadic cases) did not account for the observed distribution of cases in these sibships ($\chi^2 = 14.98$). The best estimate of p was 0.16. Estimation of x (when $p = 0.25$) yielded a value of = 0.32 suggesting that 32% of cases are considered sporadic (nongenetic), while the remaining segregate in a recessive inheritance pattern (Table I). Simultaneous iteration of p and x was not possible due to the small number of analyzable families.

DISCUSSION

Our results suggest that approximately 68% of all cases of XX gonadal (ovarian) dysgenesis in our population result from a mutant autosomal recessive gene. Autosomal recessive inheritance of at least some cases of XX gonadal (ovarian) dysgenesis initially was suggested by families with multiple affected offspring of consanguineous parents [Giusti et al., 1966; Nazareth et al., 1977; Purandare and Sathe, 1979]. A recent population-based segregation analysis in Finland by Aittomäki [1994] showed a proportion of 0.23 affected sisters, supporting autosomal recessive inheritance. In the Finnish population, the gene frequency was not only high (1:91), but most cases were identified in the north-central region of the country. It is not unexpected that a higher proportion of cases would be of genetic origin in a relatively small, isolated population.

We recognize the limitations of our analysis, in particular, our study arbitrarily restricted published cases to those published prior to 1982. We did this to minimize ascertainment bias that would inevitably occur following wide recognition of the condition, for only unusual cases would warrant publication thereafter. Isolated cases likely would be of lesser interest, leading to over-reporting of familial cases that would lead to an artificially high segregation ratio.

In multiplex families, the inheritance pattern and hence genetic counseling is straightforward. In families with a single affected individual, a recurrence risk as high as 25% is still possible and indeed likely if the parents are consanguineous. Given the probability that more than 30% of cases may be of nongenetic origin, a recurrence risk of approximately 16% (2/3 of 25%) for isolated cases of non-consanguineous seems appropriate for counseling. Nonetheless, a detailed medical history must be elicited to exclude other identifiable causes of gonadal (ovarian) dysgenesis, most of which carry very low recurrence risks. Somatic anomalies must also be sought carefully, for their presence may indicate a disorder other than XX gonadal (ovarian) dysgenesis. It is not yet clear if subtle phenotypic differences exist between the genetic and nongenetic forms of XX gonadal (ovarian) dysgenesis.

That not all cases of XX gonadal (ovarian) dysgenesis are explained by an autosomal recessive gene is not surprising. Environmental insults represent an obvious explanation in some cases. Indeed, several cases included in this study had a history of infections, including rubeola [McDonough, 1977], mumps, and chicken pox [Aleem, 1981]. However, caution must be exercised before attributing the phenotype to an infectious cause because most individuals with childhood infections do not manifest gonadal (ovarian) dysgenesis. However, existence of monozygotic twins exposed to rubeola at age two who are discordant for XX gonadal (ovarian)

TABLE I. Summary of Segregation Analysis

	Set p	Estimate p	Estimate x	Model χ^2
Null hypothesis: All autosomal recessive	.25	0.0	—	—	14.98
H_1 (no sporadics)	—	0.0	0.16	—	7.62
H_2 (sporadics allowed)	.25	—	—	0.32	5.5[a]

[a] Best χ^2.

dysgenesis [McDonough et al., 1977] lends support to the existence of an infectious cause in some individuals. Although the intrauterine environment is often assumed to be identical for monozygotic twins, there are many examples of monozygotic twins discordant for in utero exposures [Phelan, 1982; Chasnoff, 1985; Wang et al., 1990].

Several genetic mechanisms may be postulated to explain that proportion of cases not segregating in an autosomal recessive pattern. Polygenic inheritance may play a role, for any inherited defects in germ cell migration would prevent the germ cells from reaching the gonadal ridge and subsequently give rise to streak gonads. Although an extremely rare cause of autosomal recessive disorders, uniparental disomy may explain some isolated cases of XX gonadal (ovarian) dysgenesis. A contiguous gene deletion syndrome resulting in 9p monosomy has been associated with XY gonadal dysgenesis and developmental delay [Magenis, 1991]. It is possible that a gene for XX gonadal (ovarian) dys-genesis exists which could explain cases of XX gonadal (ovarian) dysgenesis with associated malformations [Maximilian, 1970; Lundberg, 1976; Skre, 1976]. The location of a gene for the autosomal recessive form of XX gonadal (ovarian) dysgenesis does not seem apparent.

Several cytogenetic causes may be hypothesized to account for some sporadic cases. Undetected mosaicism confined to the gonads, most likely for a 45,X cell line, could lead to ovarian dysgenesis. We feel this is unlikely in most cases, although the number with cytogenetic studies of multiple tissues, particularly gonads, is small. It is also plausible that an abnormal cell line could have been present early in development, but not persist. Similarly, submicroscopic deletions or other structural rearrangements may be present. One weakness in the present study is that many of the published cases were studied prior to the use of banding techniques. Rearrangements of the X chromosome are well known, but rare causes of gonadal abnormalities, with phenotypes ranging from gonadal (ovarian) dysgenesis to premature ovarian failure. Although some X chromosome rearrangements would go undetected without banding techniques, many deletions, inversions, and dicentrics would be detectable even without banding.

There is varied phenotypic expression within XX gonadal (ovarian) dysgenesis. In several multiplex families [Giusti et al., 1966; Boczkowski, 1970; Málková et al., 1974], one sister had ovarian hypoplasia and secondary amenorrhea while another had streak ovaries and primary amenorrhea. Aittomäki [1994] also observed varied expression; all affected sibs in that study had primary amenorrhea, but other presumably affected individuals related through a common ancestor had secondary amenorrhea. Overall, data suggest that the gonadal phenotype of XX gonadal (ovarian) dysgenesis may not be uniform. One must be cautious when expanding the phenotype of the syndrome; heterogeneity will become more important and the proportion of autosomal recessive cases will be expected to decrease.

ACKNOWLEDGMENTS

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